AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Withdrawn) A method of producing an antiandrogen-drug-resistant cancer cell line that expresses a mutant androgen receptor, which comprises culturing cancer cells sensitive to a specified antiandrogen drug in the presence of said antiandrogen drug, selecting a cancer cell line showing proliferation, analyzing the base sequence of the androgen receptor gene in said cancer cell line and selecting a line in which a mutation has occurred in said sequence.

2. (Withdrawn) The method of claim 1, wherein the mutation site agrees with a clinical mutation site that appears due to administration of said antiandrogen drug.

3. (Withdrawn) A method of claim 1 for producing an antiandrogen-drug-resistant cancer cell line that expresses a multiple-mutant androgen receptor, which comprises culturing cancer cells that express a mutant androgen receptor and are sensitive to a specified antiandrogen drug in the presence of said antiandrogen drug, selecting a cancer cell line showing proliferation, analyzing the base sequence of the mutant androgen receptor gene in said cancer cell line and selecting a line that has shown a different mutation in said sequence.

4. (Withdrawn) The method of claim 1, wherein the antiandrogen drug is flutamide or an analogue thereof or bicalutamide or an analogue thereof.

5. (Withdrawn) A cancer cell line that expresses a mutant androgen receptor, which is obtained by the method of claim 1.

6. (Withdrawn) A cancer cell line that expresses a multiple-mutant androgen receptor, which is obtained by the method of claim 3.

7. (Withdrawn) The cancer cell line of claim 5, which further comprises a gene under the control of an androgen-responsive promoter that permits expression analysis.

8. (Withdrawn) The cancer cell line of claim 7, wherein said gene is the prostate-specific antigen gene or a foreign reporter gene.

9. (Withdrawn) A method of screening for an antiandrogen drug that exhibits antagonistic action on the mutant androgen receptor expressed in the cancer cell line of claim 5 which comprises culturing said cancer cell line in the presence of a test substance.

10. (Withdrawn) A method of screening for an antiandrogen drug that exhibits antagonistic action on the mutant androgen receptor expressed in the cancer cell line of claim 7, which comprises culturing said cancer cell line in the presence of a test substance, and analyzing the expression of the gene under the control of then androgen-responsive promoter in said cancer cells.

11. (Withdrawn) An antiandrogen drug that exhibits antagonistic action on a mutant androgen receptor, which is selected by the method of claim 9.

12. (Previously presented) A method of screening for an antiandrogen drug that does not induce drug-resistance, which comprises:

culturing cells of an androgen-sensitive cancer in the presence of a test substance for at least six weeks; and

identifying a test substance that suppresses proliferation of said cancer cells, thereby identifying an antiandrogen drug that does not induce antiandrogen drug-resistance.

13. (Withdrawn) An antiandrogen drug having no or little potential to induce resistant cancer, which is selected by the method of claim 12.

14. (Withdrawn) The antiandrogen drug of claim 13, which has no or little potential to induce a mutation in an androgen receptor.

15. (Withdrawn) An agent for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage or the androgen-independent stage, which comprises the antiandrogen drug of claim 11.

16. (Withdrawn) A method for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage or the androgen-independent stage in a mammal, which comprises administering an effective amount of the antiandrogen drug of claim 11 to said mammal.

17. (Withdrawn) Use of the antiandrogen drug of claim 11, for the production of an agent for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage or the androgen-independent stage.

18. (Withdrawn) The cancer cell line of claim 7, wherein the androgen-responsive promoter is a PSA promoter.

19. (Withdrawn) The method of screening of claim 10, wherein the androgen-responsive promoter is a PSA promoter.

20. (Withdrawn) A kit for evaluating antiandrogen drug responsiveness of transcription factor activity of an androgen receptor or for screening an androgen receptor modulator, which comprises as a component thereof, mammalian cells containing a gene under the control of a PSA promoter that permits expression analysis.

21. (Withdrawn) The kit of claim 20, wherein the mammalian cells further expresses a specified androgen receptor.

22. (Withdrawn) The kit of claim 20, wherein a plurality of PSA promoters are tandemly ligated.

23. (Withdrawn) The kit of claim 20, wherein the gene that permits expression analysis is a prostate-specific antigen gene or a foreign reporter gene.

24. (Withdrawn) A method of evaluating antiandrogen drug responsiveness of transcription factor activity of an androgen receptor, which comprises bringing said androgen

receptor and a specified antiandrogen drug into contact with mammalian cells containing a gene under the control of a PSA promoter that permits expression analysis, and analyzing the expression of said gene.

25. (Withdrawn) A method of screening for a modulator of a specified androgen receptor, which comprises bringing said androgen receptor and a test substance into contact with mammalian cells comprising a gene under the control of a PSA promoter that permits expression analysis, and analyzing the expression of said gene.

26. (Withdrawn) The method of claim 24, wherein the contact of the androgen receptor is accomplished by the expression of said receptor in the mammalian cells.

27. (Withdrawn) The method of claim 24, wherein a plurality of PSA promoters is tandemly ligated.

28. (Withdrawn) The method of claim 24, wherein the gene that permits expression analysis is a prostate-specific antigen gene or a foreign reporter gene.

29. (Withdrawn) An isolated protein comprising the same or substantially the same amino acid sequence as the amino acid sequence of (a) the amino acid sequence of SEQ ID NO:2 in which tryptophan at amino acid number 746 is substituted by leucine, or (b) the amino acid sequence of SEQ ID NO:2 in which tryptophan at amino acid number 746 is substituted by leucine or cysteine and threonine at amino acid number 882 is substituted by alanine, or a salt thereof.

30. (Withdrawn) A partial peptide of the protein of claim 29, which comprises at least a partial amino acid sequence corresponding to a region necessary for binding with an androgen in a normal androgen receptor, or an amide thereof or an ester thereof or a salt thereof.

31. (Withdrawn) A polynucleotide comprising a polynucleotide having a nucleic acid sequence that encodes for the protein of claim 29 or the partial peptide thereof.

32. (Withdrawn) The polynucleotide of claim 31, which is a DNA.

33. (Withdrawn) The polynucleotide of claim 31, which has the following nucleic acid base sequence: (a) the nucleic acid base sequence of SEQ ID NO:1 in which the base at base number 2237 is substituted by thymine, or (b) the nucleic acid base sequence of SEQ ID NO:1 in which the base at base number 2237 or 2238 is substituted by thymine and the base at base number 2644 is substituted by guanine

34. (Withdrawn) A diagnostic agent comprising the polynucleotide of claim 31.

35. (Withdrawn) The diagnostic agent of claim 34, which is for the diagnosis of hormone-independent cancers.

36. (Withdrawn) A recombinant vector comprising the polynucleotide of claim 31.

37. (Withdrawn) A transformant transformed with the recombinant vector of claim 36.

38. (Withdrawn) An animal cell having an ability to produce the protein of claim 29.

39. (Withdrawn) The animal cell of claim 38, which is a cancer cell.

40. (Withdrawn) The animal cell of claim 39, wherein the cancer cell is a cell derived from prostate cancer.

41. (Withdrawn) A method of producing the protein or the salt thereof of claim 29, or the partial peptide, amide, ester, or the salt thereof, which comprises culturing the transformant or the animal cell expressing said protein under suitable conditions and for suitable time as to allow the same to produce the protein of claim 29 or the partial peptide thereof.

42. (Withdrawn) A method of screening a compound that alters the binding of an

androgen and the protein or the salt thereof of claim 29 or the partial peptide, amide, ester, or a salt thereof, which comprises using the protein or the salt thereof of claim 29 or the partial peptide or the amide thereof or the ester thereof or the salt thereof of claim 30.

43. (Withdrawn) A kit for screening a compound that alters the bindability of an androgen and the protein or the salt thereof of claim 29 or the partial peptide, amide, ester, or a salt thereof, which comprises the protein or the salt thereof of claim 29 or the partial peptide, amide, ester

44. (Withdrawn) An agent for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage and the androgen-independent stage, which comprises a combination of two or more kinds of antiandrogen drugs that exhibit anti-androgen action on different mutant androgen receptors.

45. (Withdrawn) The agent of claim 44, wherein one of the two or more kinds of antiandrogen drugs is selected by the method of claim 9.

46. (Withdrawn) A method for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage or the androgen-independent stage in a mammal, which comprises administering, to said mammal, an effective amount of each of two or more kinds of antiandrogen drugs that exhibit an anti-androgen action on different mutant androgen receptors.

47. (Withdrawn) The method of claim 46, wherein one of the two or more kinds of antiandrogen drugs is selected by the method of claim 9.

48. (Withdrawn) A method for making a pharmaceutical composition comprising combining two or more kinds of antiandrogen drugs that exhibit an anti-androgen action on different mutant androgen receptors, for the production of an agent for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage or the androgen-independent stage with a pharmaceutically acceptable carrier, excipient or diluent.

49. (Withdrawn) The method of claim 48, wherein one of the two or more kinds of antiandrogen drugs is selected by the method of claim 9.

50. (Withdrawn) An antibody against the protein or the salt thereof of claim 29 or the partial peptide, the amide, the ester, or the salt thereof, which does not recognize a normal androgen receptor protein or a salt thereof.

51. (Withdrawn) An isolated antibody which binds to a protein comprising the same or substantially the same amino acid sequence as in SEQ ID NO: 2 wherein tryptophan at amino acid number 746 is substituted by leucine or cysteine in the amino acid sequence, or a salt thereof, and wherein said antibody does not specifically bind, or binds with much less affinity a protein comprising the same or substantially the same amino acid sequence as in SEQ ID NO: 2 wherein threonine at amino acid number 882 is substituted by alanine in the amino acid sequence, or a salt thereof.

52. (Withdrawn) An isolated antibody which binds to a protein comprising the same or substantially the same amino acid sequence as in SEQ ID NO: 2 wherein threonine at amino acid number 882 is substituted by alanine in the amino acid sequence, or a salt thereof, and wherein said antibody does not specifically bind or binds with much less affinity a protein comprising the same or substantially the same amino acid sequence as in SEQ ID NO: 2 wherein tryptophan at amino acid number 746 is substituted by leucine or cysteine in the amino acid sequence, or a salt thereof.

53. (Withdrawn) The antibody of claim 50, which is a neutralizing antibody that suppresses a transcription factor activity of the protein.

54. (Withdrawn) A diagnostic agent comprising the antibody of claim 50.

55. (Withdrawn) The diagnostic agent of claim 54, which is for the diagnosis of transition of hormone-sensitive cancers to the androgen-independent stage.

56. (Withdrawn) A compound that alters the binding of an androgen and the protein

comprising the same or substantially the same amino acid sequence as the amino acid sequence of: (a) the amino acid sequence of SEQ ID NO:2, in which tryptophan at amino acid number 746 is substituted by leucine, or (b) the amino acid sequence of SEQ ID NO:2, in which tryptophan at amino acid number 746 is substituted by leucine or cysteine and threonine at amino acid number 882 is substituted by alanine, or the partial peptide, the amide, the ester, the salt thereof, which can be obtained using the method of screening of claim 42.

57. (Withdrawn) A pharmaceutical agent comprising the compound or the salt thereof of claim 56.

58. (Withdrawn) The pharmaceutical agent of claim 57, which is an agent for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage and the androgen-independent stage.

59. (Withdrawn) A method of quantitating the mRNA that encodes the protein of claim 29, which comprises using a polynucleotide which encodes for such protein or a portion thereof, in a screening assay.

60. (Withdrawn) A method of quantitating the protein or the salt thereof of claim 29 or the partial peptide, the amide, the ester, or the salt thereof, which comprises using the antibody of claim 50.

61. (Withdrawn) A diagnostic method for transition of hormone-sensitive cancers to the androgen-independent stage, which comprises using the quantitation method of claim 59.

62. (Withdrawn) A method of classifying antiandrogen drugs, which comprises distinguishing antiandrogen drugs, which permits generation of a resistant cancer cell line that expresses the same mutant androgen receptor by the method of claim 1, as one group, from the group consisting of antiandrogen drugs that permits generation of a resistant cancer cell line that expresses a different mutant androgen receptor.

63. (Withdrawn) An agent for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage and the androgen-independent stage, which comprises a combination of two or more kinds of antiandrogen drugs classified into different groups by the method of claim 62.

64. (Withdrawn) A method for the prophylaxis/treatment of hormone-sensitive cancers in the androgen-dependent stage or the androgen-independent stage in a mammal, which comprises administering, to said mammal, an effective amount of each of two or more kinds of antiandrogen drugs classified into different groups by the method of claim 62.

65-70. (Canceled)

71. (Previously presented) The method of claim 12, wherein the cancer cells are human cancer cells.

72. (Previously presented) The method of claim 12, wherein said cancer cells are human prostate cancer cells.

73. (Currently amended) A method of identifying an antiandrogen drug that does not induce drug resistance, which comprises:

culturing cancer cells comprising a leucine or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 in the presence of a test substance <u>for at least 6 weeks</u>; and

identifying a test substance that suppresses proliferation of said cancer cells, thereby identifying an antiandrogen drug that does not induce antiandrogen drug-resistance.

74. (Previously presented) The method of claim 73, wherein the cell further comprises an alanine substitution for threonine at amino acid number 882 of SEQ ID NO:2.

75. (Previously presented) The method of claim 73, wherein said cancer cells are human cancer cells.

76. (Previously presented) The method of claim 73, wherein said cancer cells are human prostate cancer cells.

77. (Currently amended) The method of claim 12, wherein the cells of an androgen-sensitive cancer are cultured in the presence of a test substance for at least thirteen weeks.

78. (New) The method of claim 73, wherein the cancer cells comprising a leucine or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 in the presence of a test substance are cultured in the presence of a test substance for at least thirteen weeks.